ALZHEIMER’S DISEASE IS A DEVASTATING CONDITION. This relentlessly progressive neurodegenerative disorder has no cure, it can’t be prevented, and the mean life expectancy of a person who has been diagnosed is a short seven years. The disease imposes heavy social, psychological, physical and economic burdens on caregivers, and it is costly for society: the U.S. now spends an estimated $100 billion on it every year. And costs are steadily rising with the aging of the population.

Unfortunately, despite investing billions of dollars and many years into more than 400 potential drug treatments, there are, as yet, no solutions for Alzheimer’s disease. Given that the number of people affected worldwide could quadruple to more than 100 million by 2050, we think it is time for a totally new approach: protein design.

Scientists at the University of Washington’s Institute for Protein Design have already taken the first steps to change the paradigm for Alzheimer’s disease research and treatment. We invite you to join us.

Mis-folding Proteins and Alzheimer’s Disease

Proteins are the body’s workhorses: the major functional components of living cells. However, over a person’s lifetime, otherwise normal proteins may malfunction — and may even cause toxic activity that harms the cell. Many diseases, including Alzheimer’s disease, result from a protein malfunction known as mis-folding.

Every protein consists of a long chain of amino acids, one that folds into a unique shape that allows it to interact with other proteins and molecules. One such protein, called APP, plays critical roles in brain neuron growth and repair. After fulfilling its functions, APP leaves behind scraps of amyloid-beta peptide. In Alzheimer’s disease, these scraps mis-fold, stick together in toxic clumps and aggregate to form large “plaques.” These plaques destroy brain neurons, causing progressive dementia and, eventually, death.

Most drugs under development for Alzheimer’s disease aim to protect neurons from plaque-initiated destruction. Led by David Baker, Ph.D., researchers at the UW Medicine Institute for Protein Design (IPD) are looking in a different direction. They intend to attack the root cause of the disease — amyloid-beta peptide mis-folding and aggregation — by partnering with colleagues in the Department of Pathology.

Power in Numbers: Foldit

The researchers’ first step is to design a totally new protein molecule that will bind effectively to amyloid-beta, preventing the scraps from binding to each other. The IPD is turning to its community of gamer-citizen-scientists, tapping into their creativity to help design and fold a series of candidate anti-amyloid proteins.

Foldit is an online game that allows players to manipulate on-screen protein puzzles, all in the hope that they will fold a protein that solves a certain medical problem like Alzheimer’s,
or the flu, or cancer. Several increasingly sophisticated Foldit puzzles for Alzheimer’s disease are being submitted to thousands of Foldit players. Researchers will take the gamers’ protein-design solutions, reviewing and assessing them to find the most promising and stable protein structures for binding to amyloid-beta. The best candidates will receive further evaluation and testing.

After evaluation of promising protein designs, the scientists will take the next step: replicating these designs in the lab. If a protein folds well and binds to beta-amyloid, scientists will then test it in animal models of the disease — tiny worms and mice engineered to make amyloid inappropriately.

If the research progresses as expected, scientists at UW Medicine hope to test new proteins in animal models in just a few years — and to work with human volunteers several years after that to test the protein's safety and efficacy.

**Investing in the Alzheimer’s Disease Protein Design Project**

Private philanthropy is critical to the initial stages of the Alzheimer’s Disease Protein Design Project, and we have listed several investment opportunities. Gifts of any size are welcome to reach the monetary goals listed below.

<table>
<thead>
<tr>
<th>Investment Opportunity</th>
<th>Amount</th>
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<tr>
<td>Essential Materials</td>
<td>$25,000</td>
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<td>Gifts will support the purchase of supplies: synthetic genes encoding designed anti-amyloid proteins and microfluidic chip supplies to test new proteins.</td>
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<tr>
<td>Training the Next Generation</td>
<td>$50,000</td>
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<tr>
<td>Gifts will help us train the next generation of graduate students to be protein-design experts; at the same time, students help UW Medicine conduct transformative research.</td>
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<tr>
<td>Infrastructure</td>
<td>$250,000</td>
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<td>Gifts will help us purchase the computing hardware and wet lab equipment needed to design proteins.</td>
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**Join Us**

If you are interested in making a gift, or if you would like to learn more about our work, please contact Katherine Cardinal, senior director for philanthropy, at 206.616.0412 or cardinal@uw.edu. You may also visit ipd.uw.edu for more information. Thank you for your interest in Alzheimer’s disease and protein design.

**David Baker, Ph.D.**

*UW Professor of Biochemistry; Director, UW Medicine Institute for Protein Design*

Dr. David Baker is a computational biologist who studies the three-dimensional structure of proteins. He is a member of the National Academy of Sciences and a Howard Hughes Medical Institute investigator. His team developed the Rosetta algorithm for protein structure prediction, the distributed computing project, Rosetta@home, and the Foldit computer game. Dr. Baker earned a B.A. at Harvard and a doctorate at the University of California-Berkeley, followed by a postdoctoral fellowship at the University of California-San Francisco. Among his many honors are the 2008 Sackler International Prize in Biophysics and fellowship in the American Academy of Arts and Sciences.